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The diagnostic and therapeutic difficulties of the recurrent lower respiratory tract infections in children with neurological disorders

Trudności w diagnostyce i leczeniu zakażeń dolnych dróg oddechowych u dzieci z chorobami neurologicznymi

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Pediatr Pol 2011; 86 (5): 474–480
© 2011 by Polskie Towarzystwo Pediatryczne
Otrzymano/Received: 3.06.2011
Zaakceptowano do druku/Accepted: 20.06.2011
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Wkład pracy autorów/Authors contribution:
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Konflikt interesu/Conflicts of interest:
Autorzy pracy nie zgłaszają konfliktu interesów

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ABSTRACT

Background and aims. Severe clinical course of the respiratory tract infections is very frequent in children with neurological disorders. The aim of this study was to establish the diagnostic and therapeutic procedures giving the best results in this group of children.

Methods. The symptoms, clinical picture, diagnostics, treatment an outcome of lower respiratory system infections in children with neurological disorders were analyzed. The patients, according to the type of neurological dysfunction, were divided into 5 groups: progressive encephalophaties, cerebral palsy, developmental delay, chromosomal anomalies and other dysmorphic syndromes, neuromuscular diseases. The patients were analyzed according to: lower respiratory tract infections risk factors, diagnostic signs of acute lower respiratory tract infections, outcome and treatment.

Results. In the study group the most numerous were children with cerebral palsy and with progressive encephalopaties. Those patients required target, broad-spectrum antibiotic therapy, intensive chest physiotherapy, energetic and metabolic deficits supplementation, using prokinetics and careful administration of mucolitics.

Conclusions. In the treatment of the respiratory tract diseases in children with neurological disorders cooperation of pneumologist, neurologist, gastrologist and physioterapeutist is necessary.

Keywords: cerebral palsy, progressive encephalophaties, neuromuscular diseases, neurologically disabled children, lower respiratory tract infections

STRESZCZENIE

Wstęp. Przebieg zakażeń układu oddechowego u dzieci z zaburzeniami neurologicznymi często jest bardzo ciężki, a rokowanie niepewne. Celem badania była próba ustalenia procedur diagnostycznych i terapeutycznych w nawracających infekcjach dróg oddechowych w tej grupie pacjentów.

Cel. Ciężki przebieg kliniczny zakażeń dróg oddechowych jest bardzo częsty u dzieci z zaburzeniami neurologicznymi. Celem badania było ustalenie procedur diagnostycznych i terapeutycznych, które dają najlepsze efekty w tej grupie dzieci.

Materiał i metody. W zależności od rodzaju schorzenia neurologicznego pacjentów podzielono na 5 grup: z postępującymi encefalopatiami, mózgowym porażeniem dziecięcym, opóźnieniem rozwoju psychoruchowego, aberracjami chromosomalnymi i innymi zaburzeniami dysmorficznymi oraz z chorobami nerwowo-mięśniowymi.W analizie uwzględniono czynniki ryzyka, objawy, diagnostykę, terapię i wyniki leczenia nawracających zakażeń dróg oddechowych u dzieci z przewlekłymi zaburzeniami neurologicznymi.

Wyniki. W leczeniu chorób układu oddechowego u dzieci z zaburzeniami neurologicznymi niezbędna jest ścisła współpraca pulmonologa, gastrologa i fizjoterapeuty.

Wnioski. W leczeniu chorób układu oddechowego u dzieci z zaburzeniami neurologicznymi niezbędna jest ścisła współpraca pneumologa, neurologa, gastrologa i fizjoterapeuty.

Słowa kluczowe: mózgowe porażenie dziecięce, postępująca encefatopatia, choroby nerwowo-mięśniowe, zakażenie dolnych dróg oddechowych

Introduction

The recurrent respiratory tract infections are the most common diseases in childhood. In younger children they occur 6 to 8 times a year. Their frequency decreases with age; older children become ill less frequently, and adults get sick 2 to 4 times a year [1].

Recurrent infections are associated with the process of maturation of the respiratory and immunological systems, the way of feeding early in the life, the moment of first infection, frequency of subsequent infections and exposure to noxious agents in the environment, mainly passive smoking. Many of those factors are related to the socioeconomic status [1, 2]. Recurrent infections in children without any additional health troubles are rather mild diseases; however, pneumonia is one of the most frequent causes of hospitalization among the youngest children, reaching 40% of all admissions to hospitals. In developing countries, lower respiratory tract

infections are the fifth main death reason of children younger than 5 years [2, 3].

Feeding difficulties, often accompanied by gastroesophageal reflux (GER) belong to the most important factors increasing relapse frequency and hampering the successful treatment of lower respiratory tract infections [4, 5].

A severe clinical course of acute lower respiratory tract diseases is very frequent in children with neurological disorders; however this common clinical experience is not sufficiently recorded in the literature [6, 7]. Pneumonia can often be lethal in this group of patients, among severely disabled children, up to 80% of deaths is caused by respiratory problems [7, 8].

Although it is a common clinical knowledge that children with neurological impairment often have respiratory problems, frequency rates have not been estimated. Retrospective prevalence of pneumonias estimates about 31% per 6 months; from 38% single episodes to 19% recurrent pneumonias per year [9].

A number of factors contribute to respiratory difficulties in handicapped children; several of these issues coexist and may interact with each other. Many disorders as bronchopulmonary dysplasia (BPD), malnutrition, dysphagia, GER, chest wall and spinal deformities, some antiepileptic and myorelaxant drugs as well as several others have been considered as lower respiratory infections contributing factors in this group of children [6,8]. Although most of these factors occur in all handicapped children, their relative importance varies between particular groups of patients [10–17]. In this paper, we tried to find the most important differences in clinical practice.

The aim of this study was to establish diagnostic and therapeutic procedures giving the best results in this group of children. The authors analyzed the clinical course, diagnostics, outcome and treatment of lower respiratory tract infections in children with chronic neurological disorders.

Materials and Methods

The group consisted of 72 children, 30 girls and 42 boys, aged from 2 months to 17 years (mean age 3.4 years), with a chronic neurological disorders and recurring lower respiratory tract infections, hospitalized in the Pulmological and Neurological Wards of Silesian Medical University School.

According to the type of neurological dysfunction, the patients were divided into 5 groups (Tab. I):

1. Progressive encephalophaties (PE) n=23 (32%), aged from 2 months to 13 years (mean age 2.7 years). Into this group patients with following diseases were included: globoid cell leukodystrophy (n=1), GM1 gangliosidosis (n=2), metachromatic leukodystrophy (n=1), Niemann-Pick type A disease (n=1), mucopolisacharidosis (n=2), bifunctional protein deficiency (n=1), nonketotic hiperglicynemia (n=3), ethylomalonic aciduria (n=1), hydantoin-5-propionic aciduria (n=1), Canavan disease (n=2), congenital disorders of glycosylation (n=2), ornithine carbamylase deficiency (n=1), mitochondrial encephalomyopathy (n=4) and progressive encephalopathy of unknown origin (n=1).
2. Cerebral palsy (CP); n=20 (28%), aged 1.5–17 years (mean age 5.7 years). There were 12 patients with spastic diplegia, 4 with hemiplegia and 4 with athetoid quadriplegia.
3. Developmental delay (DD); n=12 (17%), aged 2–13 months (mean age 6 months).
4. Chromosomal anomalies and other dysmorphic syndromes (CAODS) n=11; (15%) aged 7 months–6 years (mean age 2.5 years). This group comprised children with: Down syndrome (n=4), Turner syndrome (n=1), Angelman syndrome (n=3), Rett syndrome (n=1) and Wolf-Hirshorn syndrome (n=2).
5. Neuromuscular diseases (ND) n=6 (8%), aged 6 months–15 years (mean age 5.3 years). Into this group patients with spinal muscular atrophy (n=2), muscular progressive dystrophy (n=2) and polyneuropathies (n=2) were included.

Table I. Types of neurological dysfunction
Tabela I. Rodzaje zaburzeń neurologicznych

Type of neurological dysfunction	n (%)
Progressive encephalopathies	23 (32%)
Cerebral palsy	20 (28%)
Developmental delay	12 (17%)
Chromosomal anomalies and other various dysmorphic syndromes	11 (15%)
Neuromuscular disease	6 (8%)

The patients were analyzed according to:

1. Risk factors for recurrent lower respiratory tract infections:
   a. Perinatal pathology: congenital pneumonia, bronchopulmonary dysplasia (BPD), respiratory distress in the neonatal period, congenital heart defects.
   b. Factors due to underlying neurological disorder: muscular hypotonia, chest wall deformity causing retention of secretion in the airways, some antiepileptic and myorelaxant drugs.
   c. Other factors intensifying respiratory disturbances: malnutrition, gastroesophageal reflux (GER), hypoproteinemia.

   d. Colonization of the respiratory tract by pathological flora
2. Diagnostic signs of acute lower respiratory tract infections: clinical symptoms (cough, tachypnoe, dyspnoea, cyanosis), physical examination (decreased breath sounds, rales or wheezes), laboratory findings and X-ray examination.
3. Outcome of the lower respiratory tract infections.
4. Treatment.

Results

In the study group, children with PE (n=23; 32%) and CP (n=20; 28%) were the most numerous, and the least frequent were patients with neuromuscular diseases (n=6; 8%).

As the risk factors of recurrent lower respiratory tract infections, perinatal disorders, including respiratory distress syndrome, congenital pneumonia, BPD and congenital heart defects were analysed. Respiratory distress syndrome was the most frequent in children with DD (n=8; 67%) and CP (n=12; 60%). Also congenital pneumonia was most often diagnosed in children with DD (n=8; 67%) and CP (n=10; 50%), whereas less frequently – in children with PE. BPD was the most frequent in the group of children with CP (n=7; 35%).

A congenital heart defects were most frequent in the group of children with CAODS (82%), whereas they did not occur in the groups with PE, DD and ND. A relatively high incidence of respiration distress in the neonatal period in children with CAODS may be associated with the presence of other congenital defects (mainly heart, respiratory and gastrointestinal system). Perinatal pathology was not observed in the group with neuromuscular diseases (Tab. II).

Among factors determining the recurrence of respiratory tract infections resulting from a neurological condition: muscular hypotonia, weakness of respiratory muscles, adverse drug reactions (some antiepileptic and myorelaxant medicines) were analysed. Muscular hypotonia occurred most often in children with ND (n=5; 95%) and with EP (n=18; 85%); least frequent was in patients with CP. Chest deformation was most often observed in the group with ND (n=4; 66%), least frequent was in the group with DD (n=2; 16%); in the other groups chest deformities were found in approx. 40% of children. The antiepileptic and myorelaxant drugs (mainly benzodiazepines and phenobarbital) were applied in children in all groups, except for ND, most often in patients with CP and PE (Tab. III).

The factors promoting recurrent infections of the lower respiratory tract include: the body mass deficiency (most severe in the groups with PE; n=17;

Table II. Perinatal pathology
Tabela II. Patologia okresu ciążowo-porodowego

Study group	Respiratory distress	Congenital pneumonia	Congenital heart defects	BPD
Progressive encephalopathies	9 (43%)	2 (10%)	4 (13%)	2 (9%)
Cerebral palsy	12 (60%)	10 (50%)	3 (15%)	7 (35%)
Developmental delay	8 (67%)	8 (67%)	0	2 (16%)
Chromosomal anomalies and other various dysmorphic syndromes	6 (55%)	2 (18%)	9 (82%)	2 (18%)
Neuromuscular diseases	0	0	0	0

Table III. Incidence of neurological disorders
Tabela III. Częstość występowania zaburzeń neurologicznych

Study group	Muscular hypotonia	Medication	Chest deformation
Progressive encephalopathies	18 (85%)	13 (62%)	7 (33%)
Cerebral palsy	4 (20%)	12 (60%)	9 (45%)
Developmental delay	9 (75%)	5 (42%)	2 (16%)
Chromosomal anomalies and other various dysmorphic syndromes	7 (63)%	4 (36%)	5 (45%)
Neuromuscular diseases	5 (95%)	0	4 (66%)

74% and CAODS; n=8; 73%), gastroesophageal reflux and hypoproteinemia. GER was most frequently diagnosed in children with DD (n=8; 67%) and with PE (n=11; 48%). A high GER incidence in the first group may be connected with the age range and the existence of physiological reflux and in the patients. Hypoproteinemia was most often observed in the group with PE (n=10; 43%). An important factor responsible for the recurrence of respiratory tract infections is colonization of the airways by pathogenic flora. Such colonization was most often observed in children with neuromuscular diseases, which mainly resulted from a long-term course of the underlying disease and frequent hospitalizations (also in the intensive care units), due to a severe course of infections (Tab. IV).

The relapses of lower respiratory tract infections in children with neurological diseases manifested as respiration disorders with dyspnoea. Radiologically confirmed pneumonia was most often diagnosed in children with PE and ND. Dyspnoea was the least frequent in children with CP.

The recurrent lower respiratory tract infections in children with chronic neurological disorders often had a severe course and led to respiratory and circulatory insufficiency, mainly in patients with PE and ND. Circulatory failure, present mostly in children with PE, mainly with mitochondrial encephalomyopathies, lysosomal diseases and congenital disorders of glycosylation, was probably due to cardiomyopathy seen in those patients (Tab. V).

Lower respiratory tract infections required an intense treatment based on antibiotics, systemic corticosteroids, mucolytics, cardiovascular drugs and aerosol therapy. Corticosteroids were most often used in the groups of children with PE and DD (Tab. VI).

Antireflux management was most frequently introduced in the group with DD and PE. Albumin infusions were necessary mainly in children with PE and CAODS.

Discussion

Respiratory tract infections belong to the most common diseases in children. In younger patients morbidity is much higher than in older ones [18]. In developing countries, respiratory tract infections belong to main death causes of children under the age of 5. Pneumonia is a reason for hospitalization in 40% infants, still remains a serious health problem, especially in the youngest children and in so called 'high risk groups' including children with neurological diseases [2, 4, 9, 19]. Diagnostic and therapeutic difficulties concerning pneumonia in the youngest children, are potentiated by the course and complications of the underlying neurological disease [6, 7, 10–17].

Epidemiological data suggest that viruses, mainly rhinoviruses, are principal pathogens causing respiratory tract infections in children [1, 3]. Bacterial superinfections usually follow a primary viral disease. This type of infection is caused mainly by

Table IV. Incidence of factors intensifying respiratory disturbances
Tabela IV. Częstość występowania czynników nasilających zaburzenia układu oddechowego

Type of dysfunction	Ger n (%)	Malnutrition n (%)	Hipoproteinemia n (%)
Study group	31 (43%)	43 (60%)	20 (28%)
Progressive encephalopathies	11 (48%)	17 (74%)	10 (43%)
Cerebral palsy	8 (40%)	9 (45%)	2 (10%)
Developmental delay	8 (67%)	5 (42%)	3 (25%)
Chromosomal anomalies and other various dysmorphic syndromes	2 (18%)	8 (73%)	4 (36%)
Neuromuscular diseases	2 (33%)	4 (67%)	1 (17%)

Table V. Outcome of the lower respiratory tract infections
Tabela V. Powikłania infekcji dolnych dróg oddechowych

Study group	Progressive encephalopathies	Cerebral palsy	Developmental delay	Chromosomal anomalies and other various dysmorphic syndromes	Neuromuscular diseases
Respiratory failure	16 (65%)	3 (15%)	4 (33%)	4 (36%)	4 (67%)
Circulatory failure	8 (48%)	1 (5%)	1 (8%)	4 (36%)	2 (33%)

Table VI. Treatment of the lower respiratory tract infections
Tabela VI. Leczenie zakażeń dolnych dróg oddechowych

Study group	Polytherapy	>14 days	Systemic corticosteroids	Aerosolotherapy	Mucolitics
Progressive encephalopathies	18 (74%)	20 (83%)	18 (78%)	15 (65%)	3 (13%)
Cerebral palsy	10 (50%)	12 (60%)	7 (35%)	10 (50%)	12 (60%)
Developmental delay	7 (58%)	6 (50%)	6 (50%)	8 (67%)	3 (25%)
Chromosomal anomalies and other various dysmorphic syndromes	9 (82%)	9 (82%)	3 (27%)	8 (73%)	8 (73%)
Neuromuscular diseases	5 (83%)	4 (67%)	2 (33%)	5 (83%)	5 (83%)

Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus and *Moraxella catarrhalis. Mycoplasma pneumoniae* and *Chlamydia pneumoniae* should also be considered as pathogenic factors [18].

In patients with neurological disorders, pneumonia often develops on the base of chronic inflammation caused by neonatal respiratory disorders, airway colonization by pathogens, cardiovascular and respiratory congenital defects, muscular hypotonia, spine and chest deformity and increasing mucous retention in the airways [2, 6, 20].

Physical examination in contrast to symptoms and radiographic findings, usually reveals minimal abnormalities for these pneumoniae. The evaluation of respiratory murmur during physical examination is hindered by common in most children auscultatory changes connected with bronchopulmonary dysplasia, airway flaccidity or obturation accompanying GER. It is also necessary to differentiate between crepitation and fine rales – these sounds occur not only during inflammation, but also in circulatory insufficiency and transudates due to hypoalbuminemia [1, 10, 11, 13, 21].

There are not many publications regarding recurrent respiratory system infections in children with impairment of the nervous system, analysing not only the well-known and extensively discussed risk factors, but also a relationship between recurrent pneumonias and the nature of underlying neurological disease, like in the presented study.

In the study group, the most numerous were patients with PE and CP, while the least frequent were those with ND. Our results differ from data reported by other authors. Sullivan et al investigated children with severe neurological impairment and recurrent pneumonias, between their patients almost three quarters had cerebral palsy [22]. Also in studies conducted by Mahon and Kibirige majority of patients (62%) was diagnosed as suffering from cerebral palsy [9]. A large number of patients with progressive encephalopathies in our study, despite a low incidence of these diseases in the whole population, are most likely associated with frequent hospitalizations in our tertiary referral centers due to increasing neurological disability, coexistence of refractory epilepsy and recurrent infections of the lower respiratory tract. A relatively small size of the group with ND is due to an early diagnosis, often before the full clinical manifestation of characteristic for this group muscular hypotonia. In the case of severe respiratory tract infections, patients with ND are usually treated in paediatric departments, and if respiratory insufficiency occurs, in the intensive care units [23, 24].

Between risk factors for recurrent pneumonias we analyzed: perinatal pathology affecting also the respiratory system and issues increasing respiratory disturbances related to an underlying neurological disorder. In children with DD and CP, in which the CNS pathology is often a consequence of foetus and infant exposure to hypoxia, BPD, respiratory distress syndrome and congenital pneumonia, were the most common. Seddon at al also found a very high incidence of perinatal pathology in patients with cerebral palsy and recurrent pneumonia [7].

Respiratory muscles weakness leads to a progressive chest deformity and kyphoscoliosis. It causes reductions in lung volume, chest wall and lung compliance, ventilation/perfusion imbalances, hypoxemia, hypercapnia and central hypoventilation. Scoliosis which developed prior to the completion of lung growth causes reduced number and complexity of alveoli as well as increased alveolar size, factors that contribute to diminished lung volume, ventilation/perfusion imbalances, and hypoxemia. Pulmonary arterial hypertension occurring with scoliosis results from hypoxic vasoconstriction and pulmonary vascular remodeling [23, 24]. Scoliosis causes mucus retention, enabling its superinfection and secondary destruction of pulmonary vessels, lungs and bronchi [24]. Chest deformation was most often observed in

the group with ND, where muscular hypotonia was most expressed, whereas least frequently was in the group with DD, which probably resulted from the age of patients – up to the end of the first year of life. In the other groups chest deformities were found in approx. 40% of children. Similar results that chest wall deformity occurs in majority of patients with neuromuscular diseases were also presented by other authors, e.g. Healy, Mahon, Paschoal [7, 9, 24].

For some, not completely understood and researched reasons, GER appears to be more common, persistent, and severe in children with neurological impairment [6, 22, 25]. Neurological dysfunction and coexisting GER lead to vomiting, impairment of ventilation and aspiration of chyme. Any material which refluxes may not be actively cleared as a result of disturbed peristalsis, and is more likely to be aspirated. As well as predisposing to chest infections, reflux episodes may provoke profound apnea and laryngeal spasm. Seddon and Khan estimated the incidence of GER in cerebral palsy from 32% to 75% [7]. In turn, Sullivan et al found GER in 1/3 of patients with chronic serious neurological impairment [22]. In our group GER was present in 43% of children, most frequently was diagnosed in patients with DD (67%) and with PE (48%). A high incidence in the first group may be connected with the age range and the existence of physiological reflux and in some of these patients.

A severe course of lower respiratory tract infections increases malnutrition, determined by, among others, the degree of nervous system dysfunction. According to Healy malnutrition affects 40–80% of children with neurological diseases. Among our patients the body mass deficiency was present in 60%, most often in the groups with PE and CAODS. Malnutrition subjects the respiratory muscles to catabolism, leading to atrophy, weakness and reduced lung function; it also enables bacterial colonization of the airways and alters a resistance to infections. In such cases, cooperation between a gastrologist, physiotherapist and speech therapist is also necessary [6, 10, 11, 13, 19, 24].

The anamnesis frequently reveals in patients with neurological dysfunction prolonged hospitalizations in neonatal period [2, 5, 7, 21]. In these patients pneumonia is caused by endogenic or nosocomial pathogens. Gram-negative bacteria (*E. coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, H.influenzae) and also Staphylococcus aureus MRSA, Streptococcus pneumoniae, Mycoplasma, Chlamydia pneumoniae, Legionella, Acinetobacter* as well as viruses are very common pathogens in this group of patients [20]. Third generation cephalosporins, imipenems, fluoroquinolones with aminoglycosides, vancomycin and macrolides should be used in treatment of lower respiratory tract infections in such cases [19, 21, 23]. Pneumonia caused by RS virus often can be lethal in neurologically handicapped children, so in the treatment of recurrent lower respiratory tract infection application of Syntagis should be considered, especially in children with BPD syndrome [19].

Our findings indicate that in children with PE and neuromuscular diseases, the course of lower respiratory tract infections is the most severe. In these patients there are numerous coexisting factors that significantly hinder effective treatment. In children with EP, the most important factors involve: muscle hypotonia, malnutrition, adverse effects of used medicines, GER and hypoproteinemia.

The significance of individual risk factors of recurrent lower respiratory tract infections is different in children with neuromuscular diseases, where a predominant factor is muscle hypotonia, followed by chest deformity, malnutrition and colonization of the airways by pathological flora.

Our findings not only enrich the knowledge on lower respiratory tract infections in children with chronic neurological disorders, but also have significant practical implications since they indicate the main problems in the treatment of respiratory tract infections in children with nervous system dysfunction.

Conclusions

A complex treatment of recurrent lower respiratory tract infections in children with chronic diseases of the nervous system should include:

1. Elimination of deficiencies and disturbances such as hypoproteinemia, energy deficiency or electrolyte imbalance and the concomitant treatment of other systemic dysfunctions, e.g. GER or cardiovascular conditions.
2. Broad-spectrum antibiotic therapy aimed at anaerobic and aerobic bacteria (due to a tendency to aspirate chyme).
3. Administration of systemic corticosteroids in the acute phase of disease.
4. Administration of β2 mimetics, cholinolytics and corticosteroids in nebulisation.
5. Careful administration of mucolytics and hypertonic saline, depending on patient's neurological condition.
6. Kinezytherapy to improve the evacuation of retained mucus and to prevent further deformities.

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